High-Dose Methylprednisolone Inhibits the OKT3-Induced Cytokine-Related Syndrome

R.		Peces
J.M.		Urrea
P.		Escalada
M.		Gorostidi
E.		González
C.		López-Larrea

Services of Nephrology and Immunology, Hospital Covadonga, Oviedo, Spain

Dr. R. Peces, Service of Nephrology, Hospital Alarcos, E-13002 Ciudad Real (Spain)

Dear Sir,

OKT3 is the most effective immunosuppressive agent currently available for prophylaxis and treatment of acute rejection of solid organ grafts. Despite its proved efficacy, significant problems remain associated with OKT3 therapy including first-dose reaction [1, 2]. The systemic reaction is characterized by chills, fever, headache, nausea, vomiting, diarrhea, dyspnea, hypotension and sometimes pulmonary edema. Recent studies in the mouse and man indicate that the first-dose response likely results from in vivo T cell activation and concomitant cytokine release, including tumor necrosis factor α (TNF α) [3-6]. As a therapeutic procedure to decrease the severity of at least some of the symptoms characteristic of this OKT3-induced reaction, we and others have associated, on an empirical basis, to the first injection of OKT3, the administration of methylprednisolone (1 mg/kg) as recommended by the manufacturer. However, the overwhelming majority of patients continue to have significant side effects.

We have recently introduced a new protocol consisting of a single dose of methylprednisolone (500 mg i.v.) administered 1 h before the first OKT3 injection [7]. Since October 1991, 5 renal transplant recipients received 5 mg OKT3 preceded by 500 mg i.v. methylprednisolone as part of the immunosuppressive therapy. OKT3 was initiated within 1-14 posttransplantation days because of delayed graft function. At the time OKT3 was started, the patients were receiving ciclosporin (5 mg/kg/day), azathioprine (100 mg/day) and prednisone (30 mg/day). During the first day of OKT3 injection, side effects were monitored and quantitated. No systemic clinical reaction was observed in any patients. The only clinical symptoms were a low grade of fever and mild headache 1-2 h following OKT3 injection. One patient presented vomiting and mild hypertension.

In 2 patients blood was drawn before initiation of methylprednisolone, 1 h after

MP OKT3
500-, 400
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Fig. 1. Concentration of TNF α in supernatant of peripheral blood mononuclear cells of 2 renal transplant patients during the first injection of OKT3. The level of TNF α during stable transplant function is 261 ± 55 pg/ml (based on 29 observations). MP = Methylprednisolone; $\bullet$ = Patient 1; $\circ$ = Patient 2.

methylprednisolone, immediately before OKT3 and 90 min after OKT3. TNF α was measured in supernatants of peripheral blood mononuclear cells (1×10^6 ml) with a sensitive bioassay [8, 9]. The results show that the spontaneous production of TNF α was inhibited 1 h after methylprednisolone, and OKT3 did not increase it (fig. 1). In both patients only a transient increase in body temperature ($< 38^\circ\text{C}$) was observed.

The fact that no patients experienced a significant systemic reaction to OKT3 and the absence of detectable TNF α implicate this cytokine as a primary etiological agent of the first-dose reaction. Thus, the use of high-dose methylprednisolone 1 h before the first OKT3 injection may provide a means for improving anti-CD3 monoclonal antibody therapy.

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